REMARKS/ARGUMENTS

Claims 7-10, 12, 19-22, 27-30, 41, 42, 45, 46, 49, 50, 53-56, 59-67, 75-81, 85, 87, 95, and 97 have been withdrawn from consideration. Claims 1, 2, 36, 40, 68, 69, 82, 83, 92, and 93 have been amended. New claims 109-113 have been added. Support for claim amendments and newly presented claims is noted herein below.

Specifically, independent claims 1, 36, 68, 82, and 92 as amended recite stabilized HSA-free pharmaceutical compositions comprising substantially monomeric interferon-beta (IFN-β) or biologically active variant thereof solubilized in a low-ionic-strength formulation having an ionic strength that is not greater than about 20 mM. Dependent claims 2, 83, and 93 have been amended accordingly to recite buffer present in a concentration range of about 1 mM to about 20 mM. Support for recitation of an ionic-strength of not more than 20 mM resides in the specification, for example, at page 6, lines 16-18. Support for a buffer concentration of about 1 mM to about 20 mM resides in the specification, for example, at page 6, lines 18-19 and in original claim 2. Independent claims 1, 36, 68, 82, and 92 have been amended to recite that the variant or mutein of IFN-β retains the ability to bind to IFN-β receptors. Support for this limitation resides in the specification on page 18, lines 23-24. Claim 40 has been amended to recite "IFN-β" as opposed to "rhIFN-β" to provide proper antecedent basis in view of its dependency upon claim 36. Claim 68 has been amended to recite "hIFN-β" as opposed to "IFN-β" to denote the correct acronym for human IFN-β as noted at page 25, line 3, of the specification. Accordingly, dependent claim 69 has been amended to recite "hIFN-β" to provide proper antecedent basis. Claim 82 has been amended to recite the acronym for interferon-β, i.e., "IFN-β" upon its subsequent use within this claim. No new matter is added by way of claim amendment.

New claims 109-113 are directed to specific embodiments of claim 1, wherein the ionic strength of the formulation is solely determined by concentration of the buffer present in the pharmaceutical composition. Support for these claims resides in the specification, for example, at page 6, lines 5-21, particularly lines 18-21. No new matter is added by way of presentation of these new claims.

The specification has been amended to provide sequence identifiers for the amino acid sequences of mature native human IFN-β (SEQ ID NO:1) and a cysteine → serine mutein thereof, wherein the cysteine residue at amino acid position 17 has been replaced with a serine residue (SEQ ID NO:2; described in the specification, for example, at page 25, lines 2-3, and in the original claims, and known in the art as the hIFN-β_{ser17} mutein; see U.S. Patent No. 4,518,584, Fig. 1 and Fig. 10). Specifically, the amino acid sequence for the mature native human IFN-β polypeptide is described in the specification as SEQ ID NO:1 as amended in the paragraphs on page 14, line 22, continuing through page 15, line 5, page 15, lines 6-21, and page 18, line 23, continuing through page 19, line 6. The amino acid sequence for the cysteine → serine mutein of the mature native human IFN-β polypeptide is described in the specification as SEQ ID NO:2, as amended in the paragraphs on page 15, lines 6-21, and on page 18, line 23, continuing through page 19, line 6. A new Sequence Listing setting forth the recited sequences is filed concurrently herewith. These sequences are disclosed in Fig. 1 and Fig. 10 of U.S. Patent No. 4,518,584, which patent was incorporated by reference in the present specification, for example, at page 19, line 19. The specification has also been amended in the paragraph at page 18, line 26, to replace the phrase "biologically activity" with the phrase "biological activity" in order to correct an obvious typographical error. No new matter is added by way of these amendments to the specification or by way of presentation of this Sequence Listing. The Examiner is respectfully requested to enter the Sequence Listing and these amendments to the specification.

Claims 1-113 are now pending in the application. Reexamination and reconsideration of these claims is respectfully requested in view of the following remarks. The Examiner's comments are addressed below in the order set forth in the Office Action.

The Objection to the Specification Should Be Withdrawn

The Office Action has objected to the specification under MPEP §608.01 for containing embedded hyperlinks and/or other forms of browser-executable code. In response, Applicants note that MPEP §608.01 specifically defines a hyperlink or a browser-executable code as "a URL placed between these symbols '< >' and 'http://' followed by a URL address." From this

language it is clear that it is not a URL which is itself objectionable, only the hyperlink that results from the enclosure of a URL within the "< >" pair or after the "http://" character string, an interpretation that is consistent with the policy goal of preventing live web links in documents on the USPTO web page that might direct a user to a commercial site over which the USPTO has no control, rather than any policy against URLs *per se*. See MPEP §608.01.

In light of the above discussion, Applicants have amended the specification to remove the occurrence of the "http://" character string prior to a URL. The URL now contained in the specification is consequently not a live web link such as a hyperlink or browser-executable code. Because this URL is not a hyperlink or browser-executable code as defined in MPEP §608.01, the objection should be withdrawn.

The Rejections of the Claims Under 35 U.S.C. §103 Should Be Withdrawn

Claims 1-6, 8, 11, 13-18, 23-26, 31-40, 43, 44, 47, 48, 51, 52, 57, 68-74, 82-84, 86, 88-94, 96, and 98-108 are rejected under 35 U.S.C. §103 over U.S. Patent No. 5,004,605 (hereinafter the Hershenson *et al.* patent) in view of *The Merck Index* (1989), p. 859, col. 2. This rejection is respectfully traversed.

Independent claims 1, 36, 68, 82, and 92, and claims directly or indirectly dependent therefrom, recite stabilized HSA-free pharmaceutical compositions comprising substantially monomeric interferon-beta (IFN-β) or biologically active variant thereof solubilized in a low-ionic-strength formulation having an ionic strength that is not greater than about 20 mM. These compositions have a pH of about 3.0 to about 5.0, plus or minus 0.5 units. Applicants respectfully submit that these compositions, and the methods for their preparation, are not taught or suggested by the Hershenson *et al.* patent, alone or in combination with the teachings of *The Merck Index*.

The Hershenson *et al.* patent teaches and claims "a therapeutically effective amount of a recombinant interferon-β protein dissolved in an inert carrier medium comprising as a stabilizer/solubilizer an effective amount either of glycerol or of polyethylene glycol polymers having an average molecular weight from about 190 to about 1600 daltons." See, for example, column 4, lines 42-48 of the Hershenson *et al.* patent. Hershenson *et al.* explain that "[t]he

pharmaceutical compositions of this invention provide a means of maintaining recombinant IFN-β in soluble form and thereby stabilizing it by use of one or more solubilizer/stabilizers of this invention." Column 6, lines 65-68. The Hershenson *et al.* patent thus requires the use of one or more solubilizers/stabilizers to maintain a solubilized interferon formulation.

Applicants respectfully submit that the Hershenson *et al.* patent teaches a purification and formulation process that necessarily results in the preparation of IFN-β compositions that have an ionic strength that exceeds that of the presently claimed IFN-β compositions wherein the IFN-β or biologically active variant thereof is solubilized in a low-ionic-strength formulation having an ionic strength that is *not greater than about 20 mM.* Thus, the Hershenson *et al.* IFN-β compositions are prepared using a process that includes as the last protein purification step a desalting or diafiltration step at a pH range of about 8.5 to 10 employing a transfer component (sodium laurate). This desalting or diafiltration step is followed by the steps of lowering the pH of the desalted pool with an appropriate acidic agent to a pH of about 2 to about 4, removing the precipitated transfer component by centrifugation and filtration; and then adding to the desalted pool an effective amount either of glycerol or of PEGs having an average molecular weight from about 190 to about 1600 daltons to stabilize/solubilize the IFN-β. See the Hershenson *et al.* patent at column 9, lines 35-49.

Example 1 of the Hershenson *et al.* patent provides a working example of their purification and formulation process. Bulk hIFN-β_{ser17} mutein is run through a series of chromatographic purification steps. The final purification step is accomplished using a 20 mM sodium phosphate buffer at pH 9.2 that contains 0.1% sodium laurate as the transfer component. See the Hershenson *et al.* patent, at col. 18, lines 63-66. The hIFN-β_{ser17} peak is collected, and the pH of this eluted fraction is then lowered quickly to pH 3.0 using 1.0 N HCl, which results in precipitation of the sodium laurate while leaving the hIFN-β_{ser17} mutein in solution (see at col. 18, line 66, continuing through line 2, col. 19). Following centrifugation and filtration to remove SDS, the filtered supernatant comprising the hIFN-β_{ser17} mutein is stabilized by adding either 25% glycerol (v/v) or 25% PEG 300 (see at col. 19, lines 3-12). In view of the steps undertaken in Example 1, which exemplifies the Hershenson *et al.* purification and formulation process,

Applicants respectfully note that the ionic strength of the final hIFN-β_{ser17} composition would be at least 44 mM, as can be seen from the following calculations.

First, the amount of NaCl present after HCl acidification (to pH 3) of 0.1% sodium laurate (pH 9) is readily calculated as follows:

Sodium Laurate (NaLaurate) MW 222
pKa =4.85

Calculation of ionized laurate at pH 9 from Henderson-Hasselbach equation:

$pH = pKa + Log([A^-]/[A])$
or $[A^-]/[A] = antilog_{10}(pH-pKa)$
$= antilog_{10}(9-4.85)$
$= 70794$
$[NaLaurate] \cong 1/222 = 4.5$ mM

Calculation of ionized species at pH 3:

$pH = pKa + Log([A^-]/[A])$
or $[A^-]/[A] = antilog_{10}(pH-pKa)$
$= antilog_{10}(3-4.85)$
$= .014$
% ionized $= 100*(0.014/1.014)$
$= 1.4\%$

Concentration of sodium laurate:

$= .014*(1/222)$
$= .06$ mM

Concentration of NaCl produced from neutralization:

$=1/0.222-.06$
$=4.5$ mM

Second, the amount of NaCl after HCl acidification (to pH 3) of 20 mM sodium phosphate (pH 9) is readily calculated as follows:

Phosphoric acid $pK_1 = 2.12$, $pK_2 = 7.21$

At pH 9.0:

$[Na_2HPO_4]/[NaH_2PO_4] = antilog_{10}(pH\text{-}pKa)$
$= antilog_{10}(9\text{-}7.21)$
$= 61$
$[Na_2HPO_4] = 20*61/62=19.7$ mM
$[NaH_2PO_4] = 19.7/61 = 0.3$ mM
$[Na^+] = 2*19.7 + 0.3 = 39.7$mM

At pH 3.0:

$[NaH_2PO_4]/[H_3PO_4] = antilog_{10}(pH\text{-}pKa)$
$= antilog_{10}(3\text{-}2.12)$
$= 7.6$
$[NaH_2PO_4] = 20*7.6/8.6 = 17.7$ mM

Concentration of NaCl produced:

$= 39.7\text{-}17.7$
$= 22$ mM

Therefore, the total amount of salts present at pH 3.0 would be as follows:

$[NaCl] = 22 + 4.5 = 26.5$ mM
$[NaH_2PO_4] = 17.7$ mM
[NaLaurate] = 0.06 mM

or, for each ionic species,

$[Na^+] = 44.2$ mM
$[Cl^-] = 26.5$ mM
$[H_2PO_4^-] = 17.7$ mM
$[laurate^-] = 0.06$ mM

Ionic strength of a solution is equal to $\frac{1}{2} \Sigma c_i z_i^2$, in which c is the concentration and z is the charge. See the specification at page 6, lines 3-5. Thus, based on these calculations, the Hershenson *et al.* composition would have an ionic strength of at least 44.23 mM.

In view of the foregoing calculations, which are based on the method of preparation disclosed in the Hershenson *et al.* patent, Applicants respectfully submit that the ionic strength of the Hershenson *et al.* IFN-β compositions would necessarily be greater than that of the presently claimed IFN-β compositions. Applicants' claimed IFN-β compositions comprise substantially monomeric IFN-β or biologically active variant thereof solubilized in a low-ionic-strength formulation that has an ionic strength that is *not greater than about 20 mM.* Preparation of IFN-β or biologically active variants thereof in a low ionic-strength formulation as taught by Applicants is not taught or suggested by the Hershenson *et al.* patent. Rather, Applicants respectfully submit that the Hershenson *et al* . patent teaches away from Applicants' claimed invention.

The Office Action also cites to *The Merck Index* in making this obviousness rejection. As previously noted of record, this secondary reference merely teaches the chemical properties of aspartic acid. It does not suggest its modification or combination with the teachings of Hershenson *et al.* to produce the compositions or methods of Applicants' claimed invention. Nor does it provide any guidance as to how to modify the combined teachings of these two references to arrive at Applicants' claimed invention.

Applicants' low-ionic-strength formulation provides for pharmaceutical compositions comprising substantially monomeric IFN-β in the absence of HSA. Even if the teachings of *The Merck Index* are combined with the teachings of the Hershenson *et al.* patent, one could not derive Applicants' claimed compositions and claimed methods, as the Hershenson *et al.* patent teaches away from low pH IFN-β compositions wherein this protein is solubilized in a low-ionic-strength formulation having an ionic strength not greater than about 20 mM.

As the combination of the teachings of these two cited references does not teach or suggest all of the limitations of Applicants' claimed invention, this rejection of the claims should be withdrawn.

The Rejections of the Claims Under 35 U.S.C. §112, Second Paragraph, Should Be Withdrawn

Claims 1-6, 8, 11, 13-18, 23-26, 31-40, 43, 44, 47, 48, 51, 52, 57, 68-74, 82-84, 86, 88-94, 96, and 98-108 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite, because the claims recite "biologically active variants" and the specification only lists preferred, not required, functional properties of these variants. This rejection is respectfully traversed.

The specification defines biologically active variants of IFN-β as retaining IFN-β activities, "particularly the ability to bind to IFN-β receptors." Assays for detecting whether a variant retains IFN-β activities are provided in the specification at page 19, lines 1-6, of the specification. Applicants respectfully submit that these claims are definite.

However, solely for the purpose of furthering prosecution, and not for reasons related to patentability, Applicants have amended the independent claims to recite that the variant has the ability to bind to IFN-β receptors. Support for recitation of this limitation resides in the specification at page 18, lines 23-24. Accordingly, these claims are also definite, and the rejection should be withdrawn.

New Claims Added

New claims 109-113 have been added. These claims are directed to specific embodiments of claim 1. All of these claims are directed to IFN-β compositions that comprise the IFN-β or biologically active variant thereof solubilized in a low-ionic-strength formulation that has an ionic strength not greater than about 20 mM, and thus these claims are non-obvious over the prior art cited herein. Furthermore, these claims include the limitation that the variant IFN-β polypeptides have the ability to bind to IFN-β receptors. Accordingly, the rejections of the claims under 35 U.S.C. §112 and §103 should not be applied to these newly added claims.

CONCLUSION

In view of the aforementioned amendments and remarks, Applicants respectfully submit that the objection to the specification and the rejections of the claims under 35 U.S.C. §103 and 35 U.S.C. §112 are overcome and that the new claims are patentable over the art cited by the

Examiner. Accordingly, Applicants submit that this application is now in condition for allowance. Early notice to this effect is solicited. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

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Lynda-Jo Pixley